**THE 35 USC §112, SECOND PARAGRAPH REJECTION OF CLAIMS 1-14.**

Independent claims 1 and 8 were rejected as confusing because the recitation of "the m iddle portion of" therein was allegedly unclear. Dependent claims 2-7 and 9-14 inherited this rejection. The Examiner suggested deleting this language from claims 1 and 8.

Claims 1 and 8 have been amended as suggested by the Examiner. As stated by the Examiner, this amendment does not narrow claims 1 or 8. Accordingly, Applicant asserts that the present amendment to claims 1 and 8 does not constitute a narrowing within the meaning of Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. ____ (2002), slip opinion R052; No. 00-1543; 5/28/02.

**THE ALLEGED DOUBLE PATENTING REJECTION OVER U.S. APPLICATION NO. 09/328,742.**

Claims 1-14 of the present application were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 12-19 of copending application no. 09/328,742. In making this rejection the Office Action admits claims 1-14 of the present application "are not identical" to the recited claims of copending application no. 09/328,742. Applicants also note that this is only a "provisional" rejection.

**THE 35 U.S.C. SECTION 102(b) REJECTION OF CLAIMS 8, 10 and 12-13 OVER U.S. PATENT NO. 5,618,955 TO MECHOULAM ET AL.**

The Office Action asserts that each and every feature and interrelationship of Applicants' claims 8, 10 and 12-13 is shown in U.S. Patent No. 5,618,955 (Mechoulam et al) in columns 7-8, the abstract and Figures 4A and 9A-9F. "It is axiomatic that for prior art to anticipate under §102 it has to meet every element of the claimed invention." Stoller v. Ford Motor Co., 18 USPQ2d 1545, 1547 (Fed. Cir. 1991).

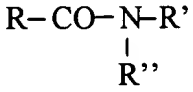
Applicants' independent claim s 1 and 8, the only independent claims in the application, each recite in pertinent part a chemical compound represented by the

structural formula:

X-Y-Z

where X, Y and Z are each members of a different Markush group.

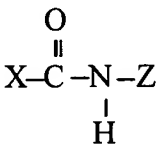
The ' 955 reference in the claims, columns 7-8 and Figures 4A and 9A-9F recites compounds of the formula:



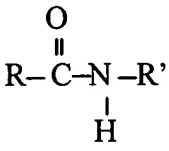
where R, R' and R' ' are each members of a different Markush group.

Ignoring for the present differences between Applicants' X member and the ' 955 R member, it is apparent that the ' 955 disclosure is only superficially similar to Applicants' claims 1 and 8 when Applicants Y member is selected as C(O)NH and the ' 955 R' ' member is selected as H. Under these conditions the compounds can be shown as:

Applicants'



' 955 reference



Applicants claims 1 and 8 each recite the Z member is selected from the group consisting of hydrogen, aryl, alkyl aryl, halogen substituted alkyl aryl, cyclic glycerols and substituted cyclic glycerols.

The ' 955 reference in Figure 4A, Figures 9A-9F and columns 7-9 teaches that R' is only $CH_2CH_2OH$. Claims 1 and 9 of the ' 955 reference (the only independent claims present) teach only that R' can be lower alkyl or $-(CH2)_{m \text{ or } p \text{ or } q \text{ or } n}-OH$, where m, p, q or n are small integers.

The ' 955 reference does NOT teach or fairly suggest that the R' group therein includes any of the members (hydrogen, aryl, alkyl aryl, halogen substituted alkyl aryl, cyclic glycerols and substituted cyclic glycerols) recited in Applicants' Z

group.

The '955 reference does not teach each and every elem ent and interrelationship of Applicants' claim s 8, 10 and 12-13. Those claims, and claims dependent therefrom, are patentable for at least this reason.

**THE 35 U.S.C. SECTION 102(b) REJECTION OF CLAIMS 1, 3, 5-6, 10 AND 12-13 OVER U.S. PATENT NO. 4,497,827 TO NELSON.**

The Office Action asserts that each and every feature and interrelationship of Applicants' claims 1, 3, 5-6, 10 and 12-13 is anticipated by U.S. Patent No. 4,497,827 to Nelson. Although the Office Action does not so state, Applicants presume this rejection also includes claim 8.

- **The Nelson reference does not anticipate each and every element of claims 8, 10 and 12-13.**

The Nelson reference only appears to anticipate Applicants' claim 8 when: X contains from 19 to 22 carbon atoms; Y is C(O)-NH- and Z is hydrogen. Claim 8 has been amended to exclude the above overlap so that the Nelson reference does not anticipate each and every feature of amended claim 8, or claims 10 and 12-13 depending from amended claim 8. Claims 8, 10 and 12-13 are patentable for at least this reason.

- **The Office Action admits that the features of claims 1, 3 and 5-6 are not explicitly anticipated by the Nelson reference.**

When the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the reference. In re Yates, 211 USPQ 1149, 1151 (CCPA 1981).

The Office Action does not indicate where the Nelson reference teaches that administration of Applicants' recited compounds would inhibit anandamide transport. The Office Action, based on the above disclosure, only asserts that " the compositions

comprising arachidonamide as taught by Nelson would inherently inhibit the transport of anandamide as claimed in instant claims 1,3,5, and 6." Thus, the Office Action implicitly admits that there is no explicit teaching or suggestion of Applicants' claimed invention in the Nelson reference and that the rejection of claims 1, 3 and 5-6 is based only on an allegedly inherent property.

- **The burden is on the Examiner to provide a basis in fact and/or technical reasoning to establish with certainty that an asserted property is inherently present in the prior art.**

The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. §§102 or 103. See MPEP §2112. However, "[t]he doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation. Probabilities are not sufficient . . . A prior inherent event cannot be established based upon speculation or where a doubt exists." Ethyl Molded Products Co. v. Betts Package Inc., 9 USPQ2d 1001, 1032-1033 (E.D. Ky. 1988). The Court of Appeals for the Federal Circuit has reinforced this position stating: "[ t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). To rely on the theory of inherency in rejecting a claim under 35 U.S.C. §§102 or 103, ". . . the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). "A nticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in the references." Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1076-1077 n12 (D. Del. 1987), aff'd 9 US PQ2d 1461 (Fed. Cir. 1989).

Further, the chemical arts are known to be unpredictable so that a person of ordinary skill is cautious about extrapolating from teachings within those arts. See, for example, In re Marzocchi, 169 USPQ 367, 368-370 (CCPA 1971), acknowledging the unpredictability within the chemical arts. This caution in extrapolating from chemical teachings is especially true when, as in the present case, the Nelson reference, at best, only alludes to a biochemical mechanism that is different from the mechanism disclosed in the pending application. In such a case, a person of ordinary skill in the art understands that the teachings are uncertain and the different mechanisms may not be related.

- **The Examiner has not met the required legal burden to establish with certainty that the Nelson reference inherently anticipates Applicants' claim s 1, 3 and 5-6.**

Inhibitors of the enzymes lipoxygenase and cyclooxygenase are effective against inflammation. See pages 539-541 from William O. Foye, Ph.D., D.Sc.(hon.), Thomas L. Lemke, Ph.D., and David A. Williams, Ph.D., *Principles of Medicinal Chemistry* (4th edition 1995) enclosed herewith.

Page 539 discloses the biosynthesis of prostaglandins from arachidonic acid (Fig. 25-3). Page 539 also discloses that inhibition of cyclooxygenase will affect prostaglandin concentration and thereby inflammation.

Page 540 discloses biosynthesis of thromboxanes, prostacyclin, and leukotrienes (Fig. 25-4). Page 540 also discloses these nonprostanoids have cardiovascular effects.

Page 541 discloses biosynthesis of leukotrienes (Fig. 25-5).

Pages 539-540 of the *Principles of Medicinal Chemistry* illustrate the "m etabolic synthetic pathways of prostaglandins, leukotrienes or thromboxanes" referred to in the Nelson reference and the Office Action. The pathways disclosed in the *Principles of Medicinal Chemistry* do NOT teach or suggest the pathway therein involves the transport of anandamide.

Further, as explained to Applicants' representative, one key point to be

understood is that these effective inhibitors have chemical structures different from each other and from the compounds of Applicants' claims. As examples, see the non-specific COX inhibitors such as aspirin (comprising a single aromatic ring); INDOMETHACIN from Merck (comprising two fused rings singly linked to a single ring); DICLOFENAC from Ciba-Geigy (comprising an aromatic ring); as well as the specific COX-2 inhibitors such as CELEBREX from Pfizer (comprising two phenyl rings individually linked to a heteroaromatic ring); VIOXX from Merck (comprising two phenyl rings individually linked to a heteroaromatic ring); or the 5-lipoxygenase inhibitor ZILEUTON from Abbott (comprising -1-(1-Benzo[b]thien-2-ylethyl)-l-hydroxyurea). Inhibitors of the enzymes lipoxygenase and cyclooxygenase have a number of chemical structures unrelated to the structures of Applicants' claim s.

The Nelson reference is concerned with simple modifications of arachidonic acid and with compounds that affect the arachidonic acid pathway illustrated in the *Principles of Medicinal Chemistry*. There is no teaching or suggestion in the Nelson reference of compounds that affect the transport of anandamide. The Nelson reference is concerned with a different biochemical pathway than involved in the transport of anandamide.

The MPEP and relevant legal precedent both mandate that to rely on the theory of inherency in rejecting a claim under 35 U.S.C. §§102 or 103, ". . . the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied art." This is especially true when the allegedly inherent characteristic is in the unpredictable field of biochemistry as is the present application.

The Office Action attempts to discharge this heavy legal burden starting at page 4, 4rth paragraph, stating:

> Nelson teaches amide derivatives of unsaturated fatty acids which are selective inhibitors of the enzymes lipoxygenase and cyclooxygenase involved in the production of pain, inflammation, bronchioconstriction and allergic reactions. The reference teaches arachidonamide and pharmaceutical compositions thereof as beneficial in the treatment of a number of inflammatory and/or painful conditions and allergic reactions

by selective inhibitory activity on the enzymes involved in the metabolic synthetic pathways of prostglandins, leucotrienes or thromboxanes. Nelson teaches amide derivatives of unsaturated fatty acids which are selective inhibitors of the enzymes lipoxygenase and cyclooxygenase involved in the production of pain, inflammation, bronchioconstriction and allergic reactions. The secondary reference teaches that these compounds are beneficial in the treatment of a number of inflammatory and/or painful conditions and allergic reactions. See: col. 1, lines 5-29; col. 3, line 24-col. 4, line 46; col. 11, line 65-col. 12, line 33.

The secondary reference teaches that Arachidonic acid is the biological precursor of such pro-inflammatory agents as prostglandins and leucotrienes, or the platelet aggregation inducers thromboxanes and that the compositions of the invention will inhibit the activity of the enzymes involved in these metabolic synthetic pathways. See: col. 1, lines 17-30 and abstract.

Therefore, the compositions comprising arachidonamide as taught by Nelson would inherently inhibit the transport of anandamide as claimed in instantly in claims 1,3,5, and 6.

Since no secondary reference has been identified in this rejection, the secondary reference cited above must be the same Nelson reference. The first paragraph above merely restates text from the Nelson reference to the effect that some fatty acid derivatives are selective inhibitors of the enzymes lipoxygenase and cyclooxygenase in some unspecified biochemical pathway and further that these compounds are beneficial in the treatment of a number of inflammatory and/or painful conditions and allergic reactions via some unspecified pathway.

The second paragraph, again merely restating text from the Nelson reference, asserts, with bracketed text added, that: " Arachidonic acid is the biological precursor of such pro-inflammatory agents as prostglandins and leucotrienes, or the platelet aggregation inducers thromboxanes and that the compositions of the [Nelson] invention will inhibit the activity of the enzymes involved in these metabolic synthetic pathways [pro-inflammatory agents as prostglandins and leucotrienes, or the platelet aggregation inducers thromboxanes]."

- The Office Action does not identify a metabolic pathway by which the Nelson compounds selectively inhibit the enzymes lipoxygenase and cyclooxygenase.

- The Office Action does not specify how selective inhibition of the enzymes lipoxygenase and cyclooxygenase is related to the anandamide transport mechanism.
- The Office Action does not identify a metabolic pathway by which the Nelson compounds allegedly provide beneficial in the treatment of a number of inflammatory and/or painful conditions and allergic reactions.
- The Office Action does not explicitly state that the compounds of Nelson must "necessarily" inhibit transport of anandam ide in an individual or animal.
- The Office Action assertion that the compounds disclosed in the Nelson reference must necessarily provide the pharmacological effects disclosed in the Nelson reference via inhibition of the anandamide transporter mechanism is contrary to the teachings in the *Principles of Medicinal Chemistry*.

Despite these failings, and despite being in what is recognized as an unpredictable art, the Office Action makes the speculative leap that the compounds disclosed in Nelson inherently, and therefore necessarily, provide an affect on the anandamide transport mechanism. Clearly, this unsupported leap of faith by the Office Action is not sufficient to meet the above-recited legal standards for rejection of a pending claim based on inherency. The Office Action does not establish a legally required basis in fact and/or technical reasoning as to why the compounds of Nelson necessarily inhibit transport of anandamide in an individual or animal.

Applicants traverse the present rejection of their claims 1,3,5-6,8,10 and 12-13 under 35 USC §102(b) as being anticipated by Nelson and assert the Examiner should withdraw the same or the provide the legally required support establishing that the compounds disclosed in the Nelson reference must necessarily inhibit transport of anandamide.

- **Claims for a new and unobvious use of a known material are patentable.**

The courts recognize the availability of process claims for new and nonobvious uses of known materials. See generally Chisum, §1.03[8][c] citing Rohm & Haas Co. v. Roberts Chemicals, 245 F.2d 693, 113 USPQ 423 (4th Cir. 1957) and In re Schoenwald, 22 USPQ2d 1671, 1673 (Fed. Cir. 1992). "Even if a composition is old, a process using a known composition in a new and unobvious way may be patentable." Loctite Corp. v. Ultraseal Ltd., 228 USPQ 90, 99 (Fed. Cir. 1985).

Applicants' claim 1, and claims dependent therefrom, is a method of inhibiting transport of anandamide in an individual or animal comprising administering to the individual or animal an amount of a recited compound. Nelson does not teach or suggest use of the compounds therein for inhibiting transport of anandamide in an individual or animal. Further, as discussed above, such a method is not inherent in the teachings of Nelson. Claims 1,3 and 5-6 are patentable for at least this reason.

Respectfully submitted,

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# Principles of Medicinal Chemistry
## Fourth Edition

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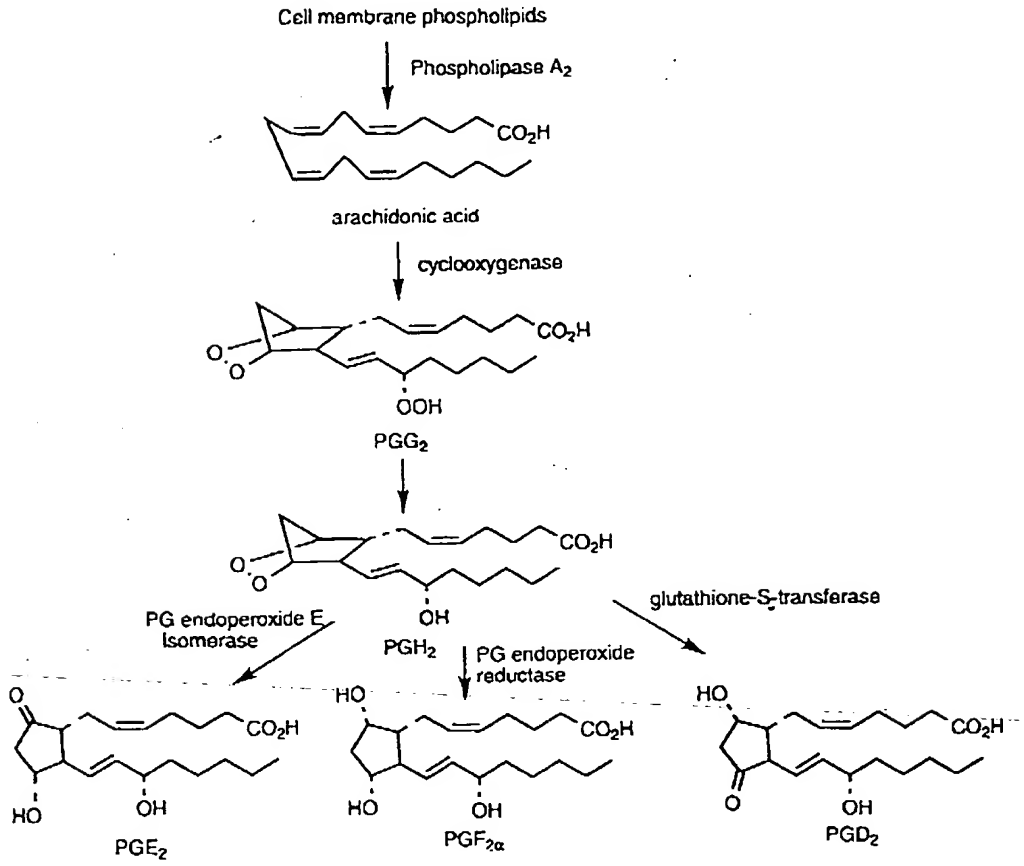


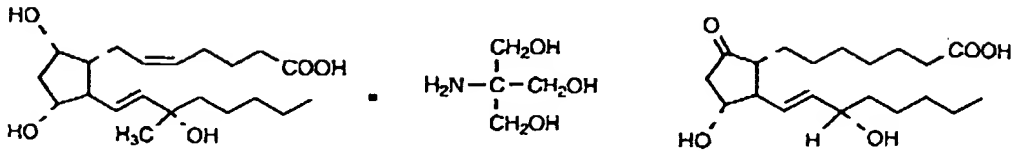

Fig. 25–3. Biosynthesis of prostaglandins from arachidonic acid.

cyclooxygenase step at which the NSAIAs inhibit PG biosynthesis preventing inflammation. Because $PGG_2$ and $PGH_2$ themselves may possess the ability to mediate the pain responses and to produce vasoconstriction, and because $PGG_2$ may mediate the inflammatory response, cyclooxygenase inhibition would profoundly reduce inflammation.

Prostaglandins are rapidly metabolized and inactivated by various oxidative and reductive pathways. The initial step involves rapid oxidation of the 15α-OH to the corresponding ketone by the prostaglandin specific enzyme 15-hydroxy-prostaglandin dehydrogenase. This is followed by reduction of the C13–14 double bond by prostaglandin $\Delta^{13}$-reductase to the corresponding dihydro ketone, which for $PGE_2$ represents the major metabolite in plasma. Subsequently, enzymes normally involved in β- and ω-oxidation of fatty acids more slowly cleave the α-chain and oxidize the C-20 terminal methyl group to the carboxylic acid derivative, respectively. Hence, dicarboxylic acid derivatives containing only 16 carbon atoms are the major metabolites of $PGE_1$ and $PGE_2$, which are excreted.

The actions of the various PGs are diverse. When administered intravaginally, $PGE_2$ will stimulate the endometrium of the gravid uterus to contract in a manner similar to uterine contractions observed during labor. Thus, $PGE_2$ is therapeutically available as dinoprostone (Prostin E2, Upjohn) for use as an abortifacient used at 12 to 20 weeks gestation and for evacuation of uterine content in missed abortion or intrauterine fetal death useful up to 28 weeks gestation. $PGE_2$ is also a potent stimulator of smooth muscle of the gastrointestinal (GI) tract and can elevate body temperature in addition to possessing potent vasodilating properties in most vascular tissue and also possessing constrictor effects at certain sites. PGEs usually cause pain when administered intradermally. Many of these properties are shared by $PGF_{2\alpha}$ which is also therapeutically available as an abortifacient at 16 to 20 weeks gestation and is marketed as dinoprost tromethamine (Prostin F2 alpha, Upjohn). The synthetic 15-methyl derivative of $PGF_{2\alpha}$, carboprost, is also available as the tromethamine salt (Prostin 15/M, Upjohn) as an abortifacient used at 13 to 20 weeks gestation. $PGF_{2\alpha}$ differs from $PGE_2$, however, in that it does not significantly alter blood pressure in humans. $PGD_2$ causes both vasodilation and vasoconstriction. Whereas the PGEs produce a relaxation of bronchial and tracheal smooth muscle, PGFs and $PGD_2$ cause contraction. $PGE_1$ is available as alprostadil (Prostin VR Pediatric, Upjohn) to maintain patency of the ductus arteriosus in neonates until surgery can be performed to correct congenital heart defects.

The effects of prostaglandins on the GI tract deserve special mention. PGEs and $PGI_2$ inhibit gastric secretion which may be induced by gastrin or histamine. PGs ap-



Carboprost tromethamine

Alprostadil

pear to play a major cytoprotecive role in maintaining the integrity of gastric mucosa. $PGE_1$ exerts a protective effect on gastroduodenal mucosa by stimulating secretion of an alkaline mucus and bicarbonate ion and also by maintaining or increasing mucosal blood flow. Thus, inhibition of PG formation in joints produces favorable results as indicated by a reduced fever, pain, and swelling, but inhibition of PG biosynthesis in the GI tract is unfavorable because it may cause disruption of mucosal integrity resulting in peptic ulcer disease which, as will be discussed later in this chapter, is commonly associated with the use of NSAIAs and aspirin.

Alternatively, nonprostanoids can also be formed from $PGH_2$ as illustrated in Figure 25–4. Thromboxane synthetase acts on $PGH_2$ to produce thromboxane $A_2$ ($TxA_2$) whereas prostacyclin synthetase converts $PGH_2$ to prostacyclin ($PGI_2$), both of which possess short biologic half-lives. $TxA_2$, a potent vasoconstrictor and inducer of platelet aggregation, has a biologic half-life of about 30 seconds, being rapidly nonenzymatically converted to the more stable, but inactive, $TxB_2$. Prostacyclin, a potent hypotensive and inhibitor of platelet aggregation, has a half-life of about 3 minutes and is nonenzymatically converted to 6-keto-$PGF_{1\alpha}$. Platelets contain primarily thromboxane synthetase whereas endothelial cells contain primarily prostacyclin synthetase. Considerable research efforts are being expended in the development of stable prostacyclin analogs and thromboxane antagonists as car-

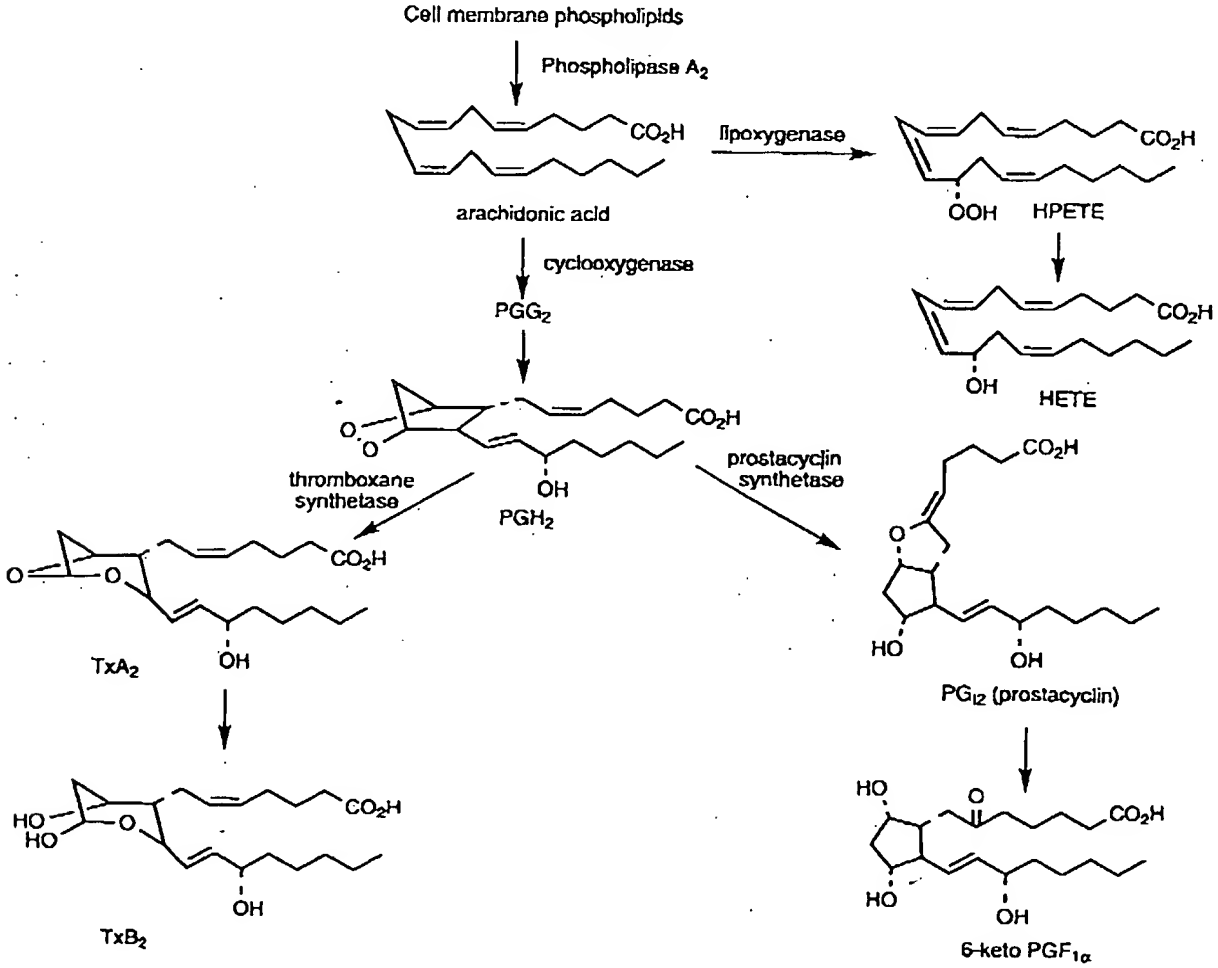



Fig. 25–4. Biosynthesis of thromboxanes, prostacyclin, and leukotrienes.

Table 25–2. Pharmacologic Properties of Prostaglandins, Thromboxanes and Prostacyclin

| | $PGE_2$ | $PGF_{2\alpha}$ | $PGI_2$ | $TxA_2$ |
|---|---|---|---|---|
| Uterus | Oxytocic | Oxytocic | | |
| Bronchi | Dilation | Constriction | | |
| Platelets | | | Inhibits aggregation | Aggregation |
| Blood vessels | Dilation | Constriction | Dilation | Constriction |

Modified from T. Nogrady, *Medicinal Chemistry—A Biochemical Approach*, 2nd ed., New York, Oxford University Press, 1988, p. 330, with permission.

diovascular agents. The pharmacologic effects of some prostaglandins, thromboxane $A_2$ and prostacyclin are summarized in Table 25–2.

The existence of distinct prostaglandin receptors may explain the broad spectrum of action displayed by the prostaglandins. The nomenclature of these receptors is based on the affinity displayed by natural prostaglandins, prostacyclin or thromboxanes at each receptor type. Thus, EP receptors are those receptors for which the PGEs have high affinity, FP receptors for PGFs, DP receptors for PGDs, IP receptors for $PGI_2$, and TP receptors for $TxA_2$. These receptors are coupled through G-proteins to effector mechanisms, which include stimulation of adenyl cyclase, and hence increased cyclic adenosine monophosphate levels (cAMP), and phospholipase C, which results in increased levels of $IP_3$ (inositol 1,4,5-triphosphate). Three distinct receptors for leukotrienes have also been identified.

Lipoxygenases are a group of enzymes which oxidize polyunsaturated fatty acids possessing two *cis* double bonds separated by a methylene group to produce lipid hydroperoxides.[20] Arachidonic acid is thus metabolized to a number of hydroperoxyeicosatetraenoic acid derivatives (HPETEs). These enzymes differ in the position at which they peroxidize arachidonic acid and in their tissue specificity. For example, platelets possess only a 12-lipoxygenase but leukocytes possess both a 12-lipoxygenase and a 5-lipoxygenase.[21] The HPETE derivatives are not stable, being rapidly converted to different metabolites. Leukotrienes are products of the 5-lipoxygenase pathway and are divided into two major classes, hydroxylated eicosatetraenoic acids (LTs) represented by $LTB_4$ and peptidoleukotrienes (pLTs) such as $LTC_4$, $LTD_4$ and $LTE_4$. The enzyme 5-lipoxygenase will produce leukotrienes from 5-HPETE as shown in Figure 25–5. LTA synthetase converts 5-HPETE to an unstable epoxide called $LTA_4$ which may

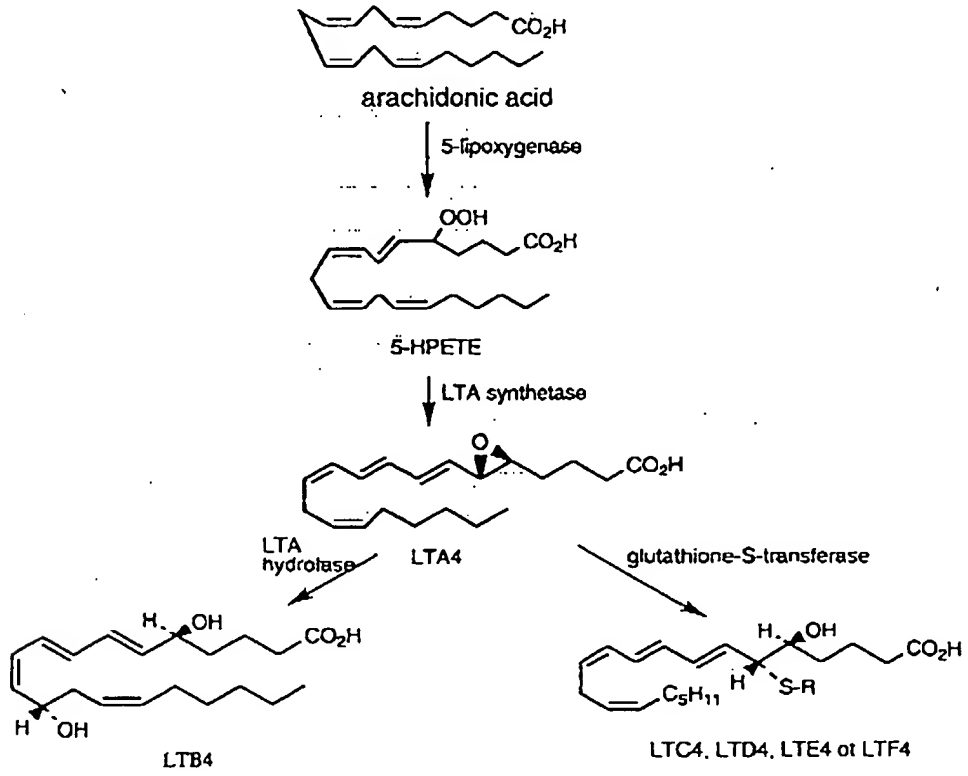



Fig. 25–5. Biosynthesis of leukotrienes.